

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
29 April 2004 (29.04.2004)

PCT

(10) International Publication Number
WO 2004/035623 A3

(15) International Patent Classification⁷: **C07K 14/575**

(21) International Application Number:
PCT/DK2003/000651

(22) International Filing Date: 2 October 2003 (02.10.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/415,626 2 October 2002 (02.10.2002) US

(71) Applicant (for all designated States except US):
ZEALAND PHARMA A/S [DK/DK]; Smedeland
26B, DK-2600 Glostrup (DK).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **EBBEHØJ, Kirsten**
[DK/DK]; 65 Skyttebjerg, DK-2850 Nærum (DK).
JEPSEN, Trine [DK/DK]; Håndværkerhaven 8, st. th.,
DK-2400 København NV (DK). **KNUDSEN, Carsten**
Boye [DK/DK]; Magnoliavej 10, DK-2670 Greve (DK).
LARSEN, Bjarne, Due [DK/DK]; Arildsgaard 5, 1. Th.,
DK-2700 Brønshøj (DK). **KNOTT, David** [GB/DK];
Ewaldsbakken 26, DK-2900 Hellerup (DK).

(74) Common Representative: **ZEALAND PHARMA A/S**;
Smedeland 26B, DK-2600 Glostrup (DK).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC,
SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA,
UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
3 June 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: STABILIZED EXENDIN-4 COMPOUNDS

(57) Abstract: The present invention disclosed compositions comprising a stabilized Exendin-4 (1-39) and related compounds. The invention describes stabilized Exendin-4 agonists that include at least one modified amino acid residue particularly at positions Gln 13, Met14, Trp25, or Asn28 of the Exendin-4 (1-39) molecule. Disclosed are preferred modifications of deaminated, hydrolyzed, oxidized, or isomerized reaction products of the specified amino acid residues corresponding to the same positions in the Exendin-4 molecule. The invention also relates to methods of making and using the stabilized Exendin compounds, such as for the treatment of diabetes.



WO 2004/035623 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/00651

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/575

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|---|
| X | WO 01 04156 A (LARSEN BJARNE DUE ;NEVE SOEREN (DK); MIKKELSEN JENS DAMSGAARD (DK)) 18 January 2001 (2001-01-18) | 1,7-11, 26-28, 36,39, 45,51-66 |
| A | claims 1-3,6,10,29-33,40-48 | 2-6, 12-25, 29-35, 37,38, 40-44, 46-50 |
| A | --- DE 196 37 230 A (BOEHRINGER MANNHEIM GMBH) 19 March 1998 (1998-03-19) page 2, line 59 - line 63 page 3, line 43 -page 4, line 16 --- -/- | 1-66 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

12 March 2004

Date of mailing of the international search report

25. 03. 2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

IDA CHRISTENSEN / ELY

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 03/00651

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | <p>WO 00 66629 A (AMYLIN PHARMACEUTICALS INC) 9 November 2000 (2000-11-09) page 9, line 29 -page 10, line 2 abstract</p> <p>---</p> | 1-66 |
| A | <p>WO 99 43708 A (MADSEN KJELD ;NOVONORDISK AS (DK); HUUSFELDT PER OLAF (DK); KNUDSE) 2 September 1999 (1999-09-02) page 32, line 1 - line 19</p> <p>-----</p> | 1-66 |

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 03/00651

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|----------------------------|---------------------|
| WO 0104156 | A | 18-01-2001 | EP 1076066 A1 | 14-02-2001 |
| | | | AT 242267 T | 15-06-2003 |
| | | | AU 5966000 A | 30-01-2001 |
| | | | CA 2378431 A1 | 18-01-2001 |
| | | | CN 1376166 T | 23-10-2002 |
| | | | DE 60003182 D1 | 10-07-2003 |
| | | | WO 0104156 A1 | 18-01-2001 |
| | | | DK 1196444 T3 | 29-09-2003 |
| | | | EP 1196444 A1 | 17-04-2002 |
| | | | EP 1329458 A2 | 23-07-2003 |
| | | | JP 2003505347 T | 12-02-2003 |
| | | | NZ 517012 A | 28-02-2003 |
| | | | PT 1196444 T | 31-10-2003 |
| | | | US 6528486 B1 | 04-03-2003 |
| | | | ZA 200200156 A | 19-05-2003 |
| ----- | | | | |
| DE 19637230 | A | 19-03-1998 | DE 19637230 A1 | 19-03-1998 |
| | | | AU 723694 B2 | 31-08-2000 |
| | | | AU 3173297 A | 05-01-1998 |
| | | | BR 9710452 A | 17-08-1999 |
| | | | CA 2257119 A1 | 11-12-1997 |
| | | | CN 1227567 A | 01-09-1999 |
| | | | WO 9746584 A1 | 11-12-1997 |
| | | | EP 0915910 A1 | 19-05-1999 |
| | | | JP 2000516912 T | 19-12-2000 |
| | | | KR 2000016389 A | 25-03-2000 |
| | | | TR 9802789 T2 | 22-03-1999 |
| ----- | | | | |
| WO 0066629 | A | 09-11-2000 | AU 4688300 A | 17-11-2000 |
| | | | BR 0010705 A | 05-02-2002 |
| | | | CA 2372214 A1 | 09-11-2000 |
| | | | CN 1372570 T | 02-10-2002 |
| | | | EP 1175443 A1 | 30-01-2002 |
| | | | JP 2002544127 T | 24-12-2002 |
| | | | WO 0066629 A1 | 09-11-2000 |
| ----- | | | | |
| WO 9943708 | A | 02-09-1999 | AU 3247799 A | 15-09-1999 |
| | | | WO 9943708 A1 | 02-09-1999 |
| | | | EP 1056775 A1 | 06-12-2000 |
| | | | JP 2003522099 T | 22-07-2003 |
| | | | US 6268343 B1 | 31-07-2001 |
| | | | US 2003199672 A1 | 23-10-2003 |
| | | | US 2001011071 A1 | 02-08-2001 |
| | | | US 2001047084 A1 | 29-11-2001 |
| | | | ZA 9901571 A | 02-09-1999 |
| ----- | | | | |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 03/00651

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **52-63**
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/DK 03/00651

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 52-63

Claims 52-63 relate to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practised on the human or animal body (PCT Rule 39.1(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds or compositions.